REMARKS

Applicants acknowledge the withdrawal of the objection to the specification and the rejection of Claim 1 under 35 U.S.C. § 102(a) and Claims 12-13 under 35 U.S.C. § 103(a) over Osada *et al.*

Applicants have cancelled Claims 1-5 without prejudice to, or disclaimer of, the subject matter contained therein. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Applicants have amended Claim 12 to depend from Claim 6 rather than canceled Claim 1. Claim 13 is amended to replace the term "an epitope tag" with the term "a tag polypeptide." Applicants have added new Claims 14-17.

Support for the amendment to Claim 13 can be found, for example, at paragraph [0229]. Support for new Claims 14-17 can be found, for example, in the claims as originally filed and paragraphs [0336], [0362], [407], and Example 18 starting at paragraph [0529].

Claims 6-8 and 11-17 are presented for examination. Applicants respond below to the rejections raised by the Examiner in the Office Action mailed on December 1, 2005.

Correction of Inventorship under 37 C.F.R. § 1.48(b)

On September 24, 2005, Applicants filed an Amendment and Response to Office Action with Exhibits 1-8 ("September 24th Amendment and Response"). On page 9 of that response, Applicants requested that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. Applicants stated that the fee as set forth in § 1.17(i) was included. In addition to the response, the filing included an Information Disclosure Statement ("IDS"), a check in the amount of $130 necessary for a deletion of inventors, a self addressed postcard, and the other required filing papers.

In the instant Office Action, the PTO responds to the request for deletion of inventors by stating that the request was deficient because "[i]t lacks the required fee under 37 C.F.R. § 1.17(i)." *Office Action* at 2.

The PTO received and cashed the $130 check for the deletion of inventors that was included with the September 24th Amendment and Response. A copy of the deposited check is

included herewith as Exhibit 1. The check was endorsed by the PTO on September 27, 2004 as evidenced by Exhibit 1. Therefore, Applicants request that the PTO delete the following inventors: Dan L. Eaton, Ellen Filvaroff, Mary E. Gerritsen, and Colin K. Watanabe.

Rejection Under 35 U.S.C. §101

The PTO maintains its rejection of pending Claims 6-8 and 11-13 under 35 U.S.C. § 101 as lacking utility for the reasons set forth in the previous Office Action. The PTO states that the asserted utility is not substantial because Applicants have not provided enough details about the differential expression of the PRO1287 mRNA; that microarrays are not reliable, citing Bustin *et al.*; that the Polakis Declaration is not relevant because only gene amplification data are presented; that the literature cautions researchers from drawing conclusions based on small changes in transcript expression, citing Hu *et al.*; and finally, that a "universal normal control" is not the proper control for the experiments, citing Saito-Hisaminato *et al.*

Utility – Legal Standard

Applicants remind the Examiner of the proper legal standard for utility. According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001), an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." The Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Also, as Applicants have previously established, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Applicants asserted utility rests on the following argument: (1) Applicants have provided reliable evidence that mRNA for the PRO1287 polypeptide is more highly expressed in normal stomach and kidney tumor tissue compared to stomach tumor and normal kidney tissue, respectively; (2) Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* a decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* a decrease; and (3) Given Applicants' evidence that the level of mRNA for the PRO1287 polypeptide is decreased in stomach tumor and normal kidney tissue, compared to normal stomach and kidney tumor tissue, respectively, it is likely that the PRO1287 polypeptide is likewise differentially expressed in stomach and kidney tumors, and therefore the claimed polypeptides are useful as diagnostic tools to distinguish tumor from normal tissue.

Applicants have established that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true. Again, the standard for establishing an asserted utility is not statistical or absolute certainty.

Substantial Utility

The PTO's Arguments Fail to Establish a Reasonable Basis to Doubt the Asserted Utility

The PTO has made essentially five interrelated arguments in support of its rejection of Applicants' asserted utility: 1. Applicants have not provided enough details about the differential expression of the PRO1287 mRNA; 2. Microarrays are not reliable, citing Bustin *et al.*; 3. The Polakis Declaration is not applicable because only gene amplification data was presented; 4. The literature cautions researchers from drawing conclusions based on small changes in transcript expression, citing Hu *et al.*; and, 5. That a "universal normal control" is not the proper control for the experiments, citing Saito-Hisaminato *et al.*

Applicants address each of these arguments in turn.

1. Applicants have provided sufficient detail to support their asserted utility

Applicants first address the PTO's argument that the evidence of differential expression of the gene encoding the PRO1287 polypeptide in stomach and kidney tumors is insufficient, and that further details are required, including baseline levels of expression, numerical values for the

level of over and underexpression, whether the results are statistically significant, and whether the results are reproducible and reliable. *See Office Action* at 5 and 9.

Applicants submit that the PTO's position that additional details are required to initially establish the utility of the claimed polypeptides is beyond that required under 35 U.S.C. §101. Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. *See In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); *M.P.E.P.* §2107.02 (III). Requests for additional evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963); *M.P.E.P.* §2107.02 (V). In addition, as stated above, the standard for establishing a utility is a low one, and statistical certainty is not required:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

Notwithstanding the presumption of utility that should be accorded to Applicants' claimed polypeptides, Applicants previously submitted a copy of a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology. As discussed previously, the declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue.

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," and that the samples were made from pooled

samples of tumor and corresponding normal tissue, increasing the accuracy of the data, thus establishing their reliability. *See Grimaldi Declaration* at ¶¶ 5 and 7.

In addition, he explains that, contrary to the PTO's assertions, "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." *Grimaldi Declaration* at ¶7. Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant, as is the baseline level of expression. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." *Id.*

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." *PTO Utility Examination Guidelines* (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the PTO's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

Finally, Applicants note that the Federal Circuit has clearly rejected a requirement that evidence of utility be numerically precise or statistically significant. In *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), the issue in the interference was whether Nelson had shown at least one utility for the compounds at issue to establish an actual reduction to practice. *Id.* at 855. The Appellants relied on two tests to prove practical utility: an *in vivo* rat blood pressure (BP) test and an *in vitro* gerbil colon smooth muscle stimulation (GC-SMS) test. In the BP test, responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect. *Id.* The Board held that Nelson had not shown adequate proof of practical utility, characterizing the tests as "rough screens, uncorrelated with actual utility." *Id.* at 856.

On appeal the C.C.P.A. reversed, holding that the Board "erred in not recognizing that tests evidencing pharmacological activity may manifest a practical utility even though they may not establish a specific therapeutic use." *Id.* (emphasis added).

Bowler argued that the BP and GC-SMS tests were inconclusive showings of pharmacological activity since confirmation by statistically significant means did not occur until after the critical date. The Court rejected this argument, stating that "a rigorous correlation is not necessary where the test for pharmacological activity is reasonably indicative of the desired response." *Id.* (emphasis added). The Court concluded that a "reasonable correlation" between the observed properties and the suggested use was sufficient to establish practical utility. *Id.* at 857 (emphasis added).

This case is of importance because the Court rejected the notion that the testing must be statistically significant to support a practical utility. *Nelson*, 626 F.2d at 857. Likewise, qualitative characterizations of a test compound as either increasing or decreasing blood pressure was acceptable. *Id.* at 855 (stating that responses were categorized as either a depressor (lowering) effect or a pressor (elevating) effect). This is the same as the data in Example 18 relied on by Applicants, where the change in mRNA levels is described as "more highly expressed." The PTO's requirement that Applicants provide numerical precision and statistical certainty to establish utility is simply wrong, and contrary to established standards for utility. Thus, these arguments do not support the PTO's position as they do not lead one skilled in the art to question Applicants' asserted utility

2. The Data in Example 18 are not Microarray Data

Applicants next address the PTO's arguments based on Bustin *et al.* that "[t]he state of the art is such that the accuracy and biological relevance of data generated from microarray techniques remain controversial." *Office Action* at 5.

These arguments are irrelevant, as Applicants are not relying on microarray data. As explained in paragraph [0530] of the specification, the differential expression of the PRO1287 mRNA was detected using the well-established technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissue samples.

This technique is more reliable than microarray data. In a recent study by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), the authors used microarray analysis combined with proteomic analysis using two-dimensional gel electrophoresis to examine changes in gene expression in leukemia cell lines. The authors report that "[c]omparison of microarray and proteomic expression profiles showed poor correlation. Use of more reliable and sensitive analyses, such as reverse transcriptase polymerase chain reaction [RT-PCR], Western blotting and functional assays, on several genes and proteins, nonetheless, confirmed that there is indeed good correlation between mRNA and protein expression." *Kuo et al.* at Abstract (emphasis added) (attached as Exhibit 2).

Thus, Bustin *et al.* offers no support for the PTO's position as it is irrelevant and does not lead one skilled in the art to question Applicants' asserted utility.

3. The Data in Example 18 are mRNA Expression Data, Not Gene Amplification Data

Applicants next address the PTO's improper rejection of the Polakis declaration. The PTO states that "the instant specification provides no information regarding increased mRNA levels of PRO1287 in tumor samples relevant to normal samples. Only gene amplification data was presented." *Office Action* at 6-7. Based on this erroneous characterization of the specification, the PTO concludes that "[t]herefore, the declaration is insufficient to overcome the rejection...since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels, and not gene amplification levels and polypeptide levels." *Id.* at 7.

These arguments are simply wrong. As explained above and in paragraph [0530] of the specification, the differential expression of the PRO1287 mRNA was detected using the well-established technique of quantitative PCR amplification of cDNA libraries isolated from different human normal and tumor tissue samples. It is well known in the art that the number of copies of a particular cDNA in the cDNA library is determined by the number of copies of the corresponding mRNA in the sample. Therefore, the amplification of cDNA libraries is used to determine the level of expression of the corresponding mRNA in the tissue – Example 18 is reporting a measure of the expression of the PRO1287 gene, *i.e.* mRNA levels, not its amplification, *i.e.* the number of copies of PRO1287 in the genome. Thus, the instant specification provides exactly the information the PTO says it was lacking – information regarding increased or decreased mRNA levels in tumor tissue compared to its corresponding

normal tissue counterpart. As Dr. Polakis states, "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." *Polakis Declaration* at ¶ 6 (emphasis added). Thus, Dr. Polakis' declaration is not only relevant, but establishes Applicants' asserted utility for the claimed polypeptides.

4. A Role for PRO1287 in Cancer is NOT Required for PRO1287 to be Useful as a Diagnostic Tool

Applicants next turn to the PTO's arguments based on Hu *et al.* that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. *See Office Action* at 7 and 10.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a published or known role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's

results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

Applicants submit that a lack of known role for the PRO1287 gene in cancer does not prevent it from being useful as diagnostic tools for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research as suggested by Hu, the encoded polypeptides and antibodies which bind to them can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO1287 gene, polypeptide and antibodies can be used as cancer diagnostic tools because the gene and polypeptide are differentially expressed in certain tumors.

Contrary to the PTO's assertion that one must know what role a gene or polypeptide plays in cancer for it to have utility, the PTO's own written policies recognize that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state: "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." *Federal Register*, Volume 66, page 1095, Comment 14. Similarly, here the disclosed nucleic acids, as well as the encoded polypeptides and related antibodies, are useful for determining whether an individual has cancer regardless of whether or not they are the cause of the cancer.

Thus, Hu *et al.* does not support the PTO's position as it does not lead one skilled in the art to question Applicants' asserted utility.

5. The Control in Example 18 is NOT a "Universal Normal Control"

Finally, Applicants address the PTO's argument that a "universal normal control" is not the proper control for the experiments. The PTO states that "[t]he 'universal normal control' in the specification is disclosed as a pooled epithelial cell sample comprising epithelial cells from liver, kidney and lung. This pooled control sample is not a proper control for determining whether a gene is overexpressed in a diseased tissue relative to a normal, matched tissue is." *Office Action* at 10. Based on Saito-Hisaminato *et al.*, the PTO argues that "the combination of liver, kidney and lung as a control would result in about 600 highly expressed genes that would not reasonably be expressed in an appropriate control, such as normal matched tissue." *Office Action* at 11.

The PTO's arguments are simply wrong. The description of Example 18 in the specification reads:

> EXAMPLE 18: Tumor Versus Normal Differential Tissue Expression Distribution
>
> Oligonucleotide probes were constructed from some of the PRO polypeptide-encoding nucleotide sequences shown in the accompanying figures for use in quantitative PCR amplification reactions. The oligonucleotide probes were chosen so as to give an approximately 200-600 base pair amplified fragment from the 3' end of its associated template in a standard PCR reaction. The oligonucleotide probes were employed in standard quantitative PCR amplification reactions with cDNA libraries isolated from different human tumor and normal human tissue samples and analyzed by agarose gel electrophoresis so as to obtain a quantitative determination of the level of expression of the PRO polypeptide-encoding nucleic acid in the various tumor and normal tissues tested. β-actin was used as a control to assure that equivalent amounts of nucleic acid was used in each reaction. Identification of the differential expression of the PRO polypeptide-encoding nucleic acid in one or more tumor tissues as compared to one or more normal tissues of the same tissue type renders the molecule useful diagnostically for the determination of the presence or absence of tumor in a subject suspected of possessing a tumor as well as therapeutically as a target for the treatment of a tumor in a subject possessing such a tumor. These assays provided the following results. *Specification* at ¶ [0530] (emphasis added).

The results in the table following this description state that the PRO1287 DNA (DNA61755-1554) is "more highly expressed in: normal stomach as compared to stomach tumor" and "kidney tumor as compared to normal kidney." **Nowhere** in the description of

Example 18 does it state that a "universal normal control" consisting of pooled epithelial cells was used.

In addition, in paragraph 5 of the first Grimaldi declaration, he states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of matching normal and tumor tissues:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual. That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. *Grimaldi Declaration* at ¶ 5 (emphasis added).

As the specification and declaration make clear, Applicants compared tumor tissue of a specific type to the corresponding normal tissue – Applicants **did not** use a "universal normal control." All of the PTO's arguments based on this incorrect characterization of Applicants' data as well as arguments based on the reference by Saito-Hisaminato *et al.* are irrelevant. Therefore, they offer no support for the PTO's position as they do not lead one skilled in the art to question Applicants' asserted utility.

Conclusion – the PTO has not offered Any Relevant Evidence or Argument which would Lead One Skilled in the Art to Question Applicants' Asserted Utility

In conclusion, the PTO has offered five arguments to support its rejection of Applicants' asserted utility as not being substantial. Applicants have addressed each of these arguments and shown that they do not support the PTO's position. Therefore, the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants have established that the Gene Encoding the PRO1287 Polypeptide is Differentially Expressed in Certain Cancers compared to the Corresponding Normal Tissue

Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that there is at least a two-fold difference in PRO1287 cDNA between stomach and kidney tumor tissue and normal stomach and kidney

tissue, respectively. Therefore, it follows that expression levels of the PRO1287 gene can be used to distinguish stomach and kidney tumor tissue from normal stomach and kidney tissue, respectively. As discussed above, the PTO has not offered any significant arguments or evidence to the contrary. As Applicants explain below, it is more likely than not that the PRO1287 polypeptide and antibodies can also be used to distinguish stomach and kidney tumor tissue from normal kidney and lung tissue, respectively.

Applicants' Evidence Establishes that a Change in mRNA Level for a Particular Gene lead to Corresponding Change in the Level of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a change in the level of mRNA for a particular protein, generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO1287 polypeptide in stomach and kidney tumor, it is likely that the PRO1287 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority

> of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." *Polakis Declaration* at ¶ 6.

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (attached as Exhibit 3, herein after Cell 3rd) and (4th ed. 2002) (attached as Exhibit 4, herein after Cell 4th)). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." *Cell 3rd* at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." *Cell 3rd* at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." *Cell 4th* at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." *Cell 4th* at 364 (emphasis added). This point is repeated on

page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." *Cell 4th* at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (attached as Exhibit 5) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), (attached as Exhibit 6), states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. *Meric et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

Additional support is also found in numerous scientific articles. For example, Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004 (attached as Exhibit 7), studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" *Zhigang* at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." *Zhigang* at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7

In a comprehensive study by Orntoft *et al.* (Mol. Cell. Proteomics. 2002; 1(1):37-45) (previously submitted), the authors examined gene amplification, mRNA expression level, and protein expression in pairs of non-invasive and invasive human bladder tumors. *Id.* at Abstract. The authors examined 40 well resolved abundant known proteins, and found that "[i]n general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations. Only one gene showed disagreement between transcript alteration and protein alteration." *Id.* at 42, col. 2. The alternations in mRNA and protein included both increases and decreases. *Id.* at 43, Table II. Clearly, a correlation in 39 of 40 genes examined supports Applicants' assertion that changes in mRNA level generally lead to corresponding changes in protein level.

In a study by Wang *et al.* (Urol. Res. 2000; 28(5):308-15) (abstract attached as Exhibit 8) the authors report that down-regulation of E-cadherin protein has been shown in various human tumors. *Id.* at Abstract. In the reported study, the authors examined the expression of cadherins and associated catenins at the mRNA level in paired tumor and nonneoplastic primary prostate cultures. They report that "[s]ix of seven cases of neoplastic cultures showed moderately-to-markedly decreased levels of E-cadherin and P-cadherin mRNA. Similar losses of alpha-catenin and beta-catenin mRNA were also observed." *Id.* As Applicants' assertion would predict, the authors state that the mRNA measures showed "good correlation" with the results from protein measures. The authors conclude by stating that "this paper presents a coordinated down-regulation in the expression of E-cadherin and associated catenins at the mRNA and protein level in most of the cases studied." *Id.*

In a more recent study by Munaut *et al.* (Int. J. Cancer. 2003; 106(6):848-55) (abstract attached as Exhibit 9) the authors report that vascular endothelial growth factor (VEGF) is expressed in 64-95% of glioblastomas (GBMs), and that VEGF receptors (VEGFR-1, its soluble form sVEGFR-1, VEGFR-2 and neuropilin-1) are expressed predominantly by endothelial cells. *Id.* at Abstract. The authors explain that infiltrating tumor cells and newly-formed capillaries progress through the extracellular matrix by local proteolysis involving matrix metalloproteinases (MMPs). In the present study, the authors "used quantitative RT-PCR, Western blot, gelatin zymography and immunohistochemistry to study the expression of VEGF, VEGFR-1, VEGFR-2, sVEGFR-1, neuropilin-1, MT1-MMP, MMP-2, MMP-9 and TIMP-2 in 20 human GBMs and 5 normal brains. The expression of these MMPs was markedly increased

in most GBMs with excellent correlation between mRNA and protein levels." *Id.* Thus, the results support Applicants' assertion that changes in mRNA level lead to corresponding changes in protein level.

In another recent study, Hui *et al.* (Leuk. Lymphoma. 2003; 44(8):1385-94 (abstract attached as Exhibit 10) used real-time quantitative PCR and immunohistochemistry to evaluate cyclin D1 mRNA and protein expression levels in mantle cell lymphoma (MCL). *Id.* at Abstract. The authors report that seven of nine cases of possible MCL showed overexpression of cyclin D1 mRNA, while two cases showed no cyclin D1 mRNA increase. *Id.* Similarly, "[s]ix of the seven cyclin D1 mRNA overexpressing cases showed increased cyclin D1 protein on tissue array immunohistochemistry; one was technically suboptimal." *Id.* The authors conclude that the study "demonstrates good correlation and comparability between measure of cyclin D1 mRNA ... and cyclin D1 protein." *Id.* Thus, this reference supports Applicants' assertion.

In a recent study by Khal *et al.* (Int. J. Biochem. Cell Biol. 2005; 37(10):2196-206) (abstract attached as Exhibit 11) the authors report that atrophy of skeletal muscle is common in patients with cancer and results in increased morbidity and mortality. *Id.* at Abstract. To further understand the underlying mechanism, the authors studied the expression of the ubiquitin-proteasome pathway in cancer patient muscle using a competitive RT-PCR to measure expression of mRNA for proteasome subunits C2 and C5, while protein expression was determined by western blotting. "Overall, both C2 and C5 gene expression was increased by about three-fold in skeletal muscle of cachectic cancer patients (average weight loss 14.5+/-2.5%), compared with that in patients without weight loss, with or without cancer. ... There was a good correlation between expression of proteasome 20Salpha subunits, detected by western blotting, and C2 and C5 mRNA, showing that increased gene expression resulted in increased protein synthesis." These findings support Applicants' assertion that changes in mRNA level lead to changes in protein level.

Maruyama *et al.* (Am. J. Patho. 1999; 155(3):815-22) (abstract attached as Exhibit 12) investigated the expression of three Id proteins (Id-1, Id-2 and Id-3) in normal pancreas, in pancreatic cancer and in chronic pancreatitis (CP). The authors report that pancreatic cancer cell lines frequently coexpressed all three Ids, "exhibiting good correlation between Id mRNA and protein levels." *Id.* at Abstract. In addition, the authors teach that all three Id mRNA levels were

expressed at high levels in pancreatic cancer samples compared to normal or CP samples. At the protein level, Id-1 and Id-2 staining was faint in normal tissue, while Id-3 ranged from weak to strong. In contrast, in the cancer tissues "many of the cancer cells exhibited abundant Id-1, Id-2, and Id-3 immunoreactivity," and Id-1 and Id-2 protein was increased significantly in the cancer cells by comparison to the respective controls, mirroring the overexpression at the mRNA level. Thus, the authors report that in both cell lines and tissue samples, increased mRNA levels leads to an increase in protein overexpression, supporting Applicants' assertion.

Support for Applicants' assertion is also found in an article by Caberlotto *et al.* (Neurosci. Lett. 1999; 256(3):191-4) (abstract attached as Exhibit 13). In a previous study, the authors investigated alterations of neuropeptide Y (NPY) mRNA expression in the Flinders Sensitive Line rats (FSL), an animal model of depression. *Id.* at Abstract. The authors reported that in the current study, that NPY-like immunoreactivity (NPY-LI) was decreased in the hippocampal CA region, and increased in the arcuate nucleus, and that fluoxetine treatment elevated NPY-LI in the arcuate and anterior cingulate cortex. The authors state that "[t]he results demonstrate a good correlation between NPY peptide and mRNA expression." Thus, increases and decreases in mRNA levels were reflected in corresponding changes in protein level.

Mizrachi and Shemesh (Biol. Reprod. 1999; 61(3):776-84) (abstract attached as Exhibit 14) investigated their hypothesis that FSH regulates the bovine cervical prostaglandin E(2) (PGE(2)) synthesis that is known to be associated with cervical relaxation and opening at the time of estrus. *Id.* at Abstract. Cervical tissue from pre-estrous/estrous, luteal, and postovulatory cows were examined for the presence of bovine (b) FSH receptor (R) and its corresponding mRNA. The authors report that bFSHR mRNA in the cervix was maximal during pre-estrus/estrus, and that the level of FSHR protein was significantly higher in pre-estrous/estrous cervix than in other cervical tissues. *Id.* The authors state that "[t]here was a good correlation between the 75-kDa protein expression and its corresponding transcript of 2.55 kb throughout the estrous cycle as described by Northern blot analysis as well as RT-PCR." *Id.* Thus, changes in the level of mRNA for bFSHR led to corresponding changes in FSHR protein levels, a result which supports Applicants' assertion.

In a study by Stein *et al.* (J. Urol. 2000; 164(3 Pt 2):1026-30) (abstract attached as Exhibit 15), the authors studied the role of the regulation of calcium ion homeostasis in smooth muscle

contractility. *Id.* at Abstract. The authors investigated the correlation between sarcoplasmic endoplasmic reticulum, calcium, magnesium, adenosine triphosphatase (SERCA) protein and gene expression, and the contractile properties in the same bladder. Partial bladder outlet obstructions were created in adult New Zealand white rabbits, which were divided into control, sham operated and obstructed groups. Stein *et al.* report that "[t]he relative intensities of signals for the Western [protein] and Northern [mRNA] blots demonstrated a strong correlation between protein and gene expression. ... The loss of SERCA protein expression is mediated by down-regulation in gene expression in the same bladder." *Id.* This report supports Applicants' assertion that changes in mRNA level, *e.g.* a decrease, lead to a corresponding change in the level of the encoded protein, *e.g.* a decrease.

In an article by Guo and Xie (Zhonghua Jie He He Hu Xi Za Zhi. 2002; 25(6):337-40) (abstract attached as Exhibit 16) the authors investigated the expression of macrophage migration inhibitory factor (MIF) in human acute respiratory distress syndrome(ARDS) by examining the expression of MIF mRNA and protein in lung tissue in ARDS and normal persons. *Id.* at Abstract. The authors report "undetectable or weak MIF mRNA and protein expression in normal lungs. In contrast, there was marked upregulation of MIF mRNA and protein expression in the ARDS lungs." *Id.* This is consistent with Applicants' assertion that a change in mRNA for a particular gene, *e.g.* an increase, generally leads to a corresponding change in the level of protein expression, *e.g.* an increase.

These studies are representative of numerous published studies which support Applicants' assertion that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit herewith an addition 70 references (abstracts attached as Exhibit 17) which support Applicants' assertion.

In addition to these supporting references, Applicants also submit herewith additional references which offer indirect support of Applicants' asserted utility by illustrating that in general mRNA and protein levels correlate well.

For example, in an article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract attached as Exhibit 18) the authors conducted a study of mRNA and protein expression in yeast. Contrary to the results of the earlier study by Gygi, Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract.

In a study which is more closely related to Applicants' asserted utility, Godbout *et al.* (J. Biol. Chem. 1998; 273(33)21161-8) (abstract attached as Exhibit 19) studied the DEAD box gene, DDX1, in retinoblastoma and neuroblastoma tumor cell lines. The authors report that "there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied." *Id.* Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Similarly, in an article by Papotti *et al.* (Virchows Arch. 2002; 440(5):461-75) (abstract attached as Exhibit 20) the authors examined the expression of three somatostatin receptors (SSTR) at the mRNA and protein level in forty-six tumors. *Id.* at Abstract. The authors report a "good correlation between RT-PCR [mRNA level] and IHC [protein level] data on SSTR types 2, 3, and 5." *Id.*

Van der Wilt *et al.* (Eur. J. Cancer. 2003; 39(5):691-7) (abstract attached as Exhibit 21) studied deoxycytidine kinase (dCK) in seven cell lines, sixteen acute myeloid leukemia samples, ten human liver samples, and eleven human liver metastases of colorectal cancer origin. *Id.* at Abstract. The authors report that "enzyme activity and protein expression levels of dCK in cell lines were closely related to the mRNA expression levels" and that there was a "good correlation between the different dCK measurements in malignant cells and tumors." *Id.*

Grenback *et al.* (Regul. Pept. 2004; 117(2):127-39) (abstract attached as Exhibit 22) studied the level of galanin in human pituitary adenomas using a specific radioimmunoassay. *Id.* at Abstract. The authors report that "[i]n the tumors analyzed with in situ hybridization there was a good correlation between galanin peptide levels and galanin mRNA expression." *Id.*

Similarly, Shen *et al.* (Blood. 2004; 104(9):2936-9) (abstract attached as Exhibit 23) examined the level of B-cell lymphoma 2 (BCL2) protein expression in germinal center (GC) B-cells and diffuse large B-cell lymphoma (DLBCL). *Id.* at Abstract. The authors report that "GC cells had low expression commensurate with the low protein expression level" and that in DLBCL the level of BCL2 mRNA and protein expression showed "in general, a good correlation." *Id.*

Likewise, in an article by Fu *et al.* (Blood 2005; 106(13):4315-21) (abstract attached as Exhibit 24) the authors report that six mantle cell lymphomas studied "expressed either cyclin D2 (2 cases) or cyclin D3 (4 cases)." *Id.* at Abstract. "There was a good correlation between cyclin

D protein expression and the corresponding mRNA expression levels by gene expression analysis." *Id.*

These examples are only a few of the many references Applicants could cite. Applicants submit herewith 26 additional references (abstracts attached as Exhibit 25) which also support Applicants' assertion in that the references report a correlation between the level of mRNA and corresponding protein, contrary to the assertion of the PTO that mRNA and protein levels are not correlated.

In summary, Applicants submit herewith a total of 118 references in addition to the declarations and references already of record which support Applicants' asserted utility, either directly or indirectly. These references support the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.*, abstracts attached as Exhibit 26). However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

In conclusion, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO1287 mRNA is differentially expressed in stomach and kidney tumors compared to their normal tissue counterparts, the PRO1287 polypeptide will likewise be differentially expressed in stomach and kidney tumors. This differential expression of the PRO1287 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly stomach and kidney cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Applicants next address the PTO's assertion that the asserted utilities are not specific to the claimed polypeptides related to PRO1287. Applicants respectfully disagree.

Specific utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO1287 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene for the PRO1287 polypeptide is differentially expressed by at least two-fold in stomach and kidney tumor tissue compared to normal stomach and kidney tissue, respectively. These data are strong evidence that the PRO1287 gene and polypeptide are associated with stomach and kidney tumors. Thus, contrary to the assertions of the PTO, Applicants submit that they have provided evidence associating the PRO1287 gene and polypeptide with a specific disease. The asserted utility for the claimed polypeptides as diagnostic tools for cancer, particularly stomach and kidney tumors, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Utility – Conclusion

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility. Instead, evidence which is "reasonably" correlated with the asserted utility is sufficient. *See Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); *Nelson v. Bowler*, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same). In addition, utility need only be shown to be "more likely than not true," not to a statistical certainty. *M.P.E.P.* at § 2107.02, part VII (2004). Considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at

least one specific, substantial, and credible utility. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of pending Claims 6-8 and 11-13 under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. *Office Action* at 12.

In addition, the PTO separately rejects pending claims 6-8 and 11-13 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the reasons of record. The PTO previously rejected only Claims 1-5 and 12-13, arguing that even if the specification were enabling for a polypeptide of SEQ ID NO:72, it "would still not reasonably provide enablement for polypeptides having at least 80%, 85%, 90%, 95% or 99% amino acid sequence identity to the polypeptide of SEQ ID NO:72." *Office Action dated 6/25/04* at 4-5.

Applicants' Specification Teaches How to Make and Use the Claimed Subject Matter

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. To the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

Applicants also note that the above arguments regarding percent sequence identity were not originally applied to Claims 6-8 and 10-11 which do not recite percent sequence identity. Applicants have amended Claims 12-13 to depend from Claim 6. Therefore, as the PTO previously acknowledged, the argument above regarding percent sequence identity is not applicable to Claims 6-8 and 11-13, and should be withdrawn.

As to new claims 14-17, these claims recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:72 in stomach or kidney tissue samples."

Applicants submit that the specification enables one skilled in the art to make and use the full scope of the claims without undue experimentation.

The specification discloses how to make the claimed polypeptides, for example in paragraphs [0283]-[0315] and Examples 6-9 (¶¶ [0453]-[0492]). In addition, methods for making polypeptides which are at least 95% identical to SEQ ID NO:72 by making substitutions or deletions are also disclosed in the specification and were well known in the art. *See e.g., Specification* at paragraphs [0256]-[0271]. Methods for making and testing antibodies for specificity were well known in the art, and are disclosed in the specification, including paragraphs [0361]-[0379] and Example 10 (¶¶ [0493]-[0499]), which specifically describes the preparation of antibodies that bind PRO polypeptides. In addition, the specification discloses that antibodies to the claimed polypeptides can be used in diagnostic assays to detect the expression of PRO1287 in specific types of tissue. *See e.g., Specification* at [0407].

In light of the differential expression of the nucleic acid encoding the PRO1287 polypeptide in stomach and kidney tumor tissues compared to normal stomach and kidney tissue, one of skill in the art would expect the PRO1287 polypeptide to be differentially expressed in these tumors as well. Therefore, given the teaching in the specification on how to make and use the claimed polypeptides to detect expression of PRO1287 in specific tissues, one of skill in the art would be enabled to practice the claimed invention without undue experimentation.

Because Appellants' specification teaches how to make and use the claimed subject matter, it must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support. *See M.P.E.P.* § 2164.04. The PTO has not offered any arguments or evidence which are applicable to Claims 14-17, and therefore has not established a *prima facie* rejection of Claims 14-17.

In conclusion, Applicants submit that the pending claims are enabled given that the specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO1287, as well as providing guidance as to how to use the claimed polypeptides as diagnostic tools. Thus, there is significant guidance how to make and use the claimed polypeptides. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific

antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide). Therefore, Applicants request that the PTO reconsider and withdraw the enablement rejection of the pending claims under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of pending Claims 6-8 and 11-13 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement for the reasons set forth in the previous Office Actions. In the earlier Office Action, the PTO rejected only Claims 1-5 and 12-13, arguing that the claims directed to at least 80%, 85%, 90%, 95% or 99% sequence identity "do not require that the encoded polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides defied only by sequence identity." *Office Action dated 6/25/04* at 6.

The Pending Claims are Adequately Described

To overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 U.S.P.Q. at 97." *M.P.E.P.* § 2163.04.

As an initial matter, Applicants note that the PTO has failed to meet its burden of rebutting the presumption that the written description is adequate for pending Claims 6-8 and 11-13 because PTO's arguments do not apply to claims which are not directed to variant polypeptides. Pending Claims 6-8 and 11-13 do not recite percent sequence identity, and therefore are adequately described by the disclosure of Figure 72, SEQ ID NO:72 and ATCC Deposit No. 203112. The PTO implicitly acknowledged this when it did not reject Claims 6-11 as lacking adequate written description in the first Office Action. Thus, the PTO should withdraw the rejection of Claims 6-8 and 11-13.

As to new Claims 14-17, they are analogous to the claims discussed in Example 14 of the written description training materials available on the PTO's website. In Example 14, the written description requirement was found to be satisfied for claims directed to polypeptides with 95% homology to a disclosed sequence that also possess a recited catalytic activity, where procedures for making variant proteins were routine in the art and the specification provided an assay for detecting the recited catalytic activity of the protein. This disclosure satisfies the written description requirement even though the applicant had disclosed only a single species and had not made any variants. The Guidelines state that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity."

Like Example 14, Claims 14-17 have very high sequence homology to the disclosed sequence and must share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:72 in stomach or kidney tissue samples. As in Example 14, at the time of the effective filing date of the instant application, it was well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. *See, e.g., Specification* at ¶¶ [0256]-[0271]. In addition, the specification discloses in detail how to make antibodies which specifically detect a particular PRO polypeptide, and how to use them to detect the PRO polypeptide in a particular tissue. *See, e.g., Specification* ¶¶ [0363]-[0379], [0407], and [0493]-[0499]. Like a particular catalytic activity, the function of being useful to produce an antibody specific to SEQ ID NO:72 is directly related to the structure of the claimed polypeptides. Thus, like Example 14, the genus of polypeptides that have at least 95% amino acid sequence identity to the disclosed sequences and possess the described functional activity are adequately described.

As to the PTO's arguments in the first Office Action that the claims "do not require that the claimed polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature," these arguments are moot in light of Claims 14-17 which were added after the first Office Action and require a conserved structure as detailed above.

In conclusion, Applicants submit that none of the PTO's arguments are applicable to pending Claims 6-8 and 11-13 which do not recite percent sequence identity. In addition, Applicants submit that they have satisfied the written description requirement for the remaining pending claims based on the actual reduction to practice of SEQ ID NO:72, by specifying a high level of amino acid sequence identity, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

CONCLUSION

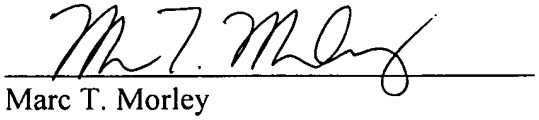
In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3/30/06

By: 

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